Review article

Rapports De Pharmacie Vol.2 (1), 2016, 163-170
ISSN: 2455-0507

A REVIEW: UTILISATION OF NANOWIRE IN NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

The emerging field of nanomedicine has been propelled by the growth and gradual overlap of disciplines such as nanotechnology, biochemistry, pharmacology, and medicine, all of which are themselves highly interdisciplinary. The new field of nanomedicine integrates advanced nanomaterials such as nanowire (NW) arrays with biomolecules, cells, and eventually organisms, in order to develop novel platforms for applications such as biosensing, drug screening, and drug delivery.In modern years, the potential and utilisation of nanowires in nanomedicine, including drug delivery and diagnostics, have been discovered by several groups.

Keywords: Nickel nanowire, Nickel ferrite nanowires, Silicon nanowire, FePd nanowires

INTRODUCTION

Nanowires are solid, crystalline rods with diameters in the nanometer range (10–100 nm) and typical lengths of around a few micrometers. These objects can be made from a wide range of inorganic materials and are occasionally termed nanorods or nanowhiskers (Fig 1).

For the past two decades, the one-dimensional nanostructures such as wires, tubes, belts and rods have been widely studied as they possess interesting and unique electronic, optical, thermal, mechanical and magnetic properties. [1]

Among the various classes of one-dimensional nanostructures, semiconductor nanowires possess several distinctive characteristics. Their ability to be combined into electronic devices, novel sub-wavelength optical phenomena, their large tolerance for mechanical deformations, their capability to interface with other microscopic and nanoscopic systems in nature, the decoupling of length scales related different physical phenomena in the radial and axial directions and their extreme surface-to-volume ratio have directed to an explosion of applications that developed these structures.

The different magnetic materials, magnetic nanowires (NWs) such as nickel nanowires (Ni NWs) are captivating candidates for cell manipulation. Due to shape anisotropy, a magnetic torque can be useful to actuate individual magnetic NWs with a low-strength magnetic field. [2-7]. Researchers have stated that Ni NWs are easily internalized by cells and no major cytotoxicity was seen due to several layers of native nickel oxide on the surface. [8-10] Moreover, it was shown that Ni NWs could be remotely heated by using radio frequency fields at 810 MHz to induce hyperthermia in living cells. [11]

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Drug discovery has also benefited from these developments with the design of new drugs and the development of high throughput screening (HTS) strategies for new molecules. Combined with drug delivery strategies based on novel nanomaterials, with better biocompatibility and target specificity, nanomedicine opens the way to a myriad of potential new therapies.

Based on these developments, there are three main impact areas foreseen for nanomedicine:

- High-quality and fast diagnosis of diseases.
- Drug discovery, with the development of fast and cheap screening strategies of potential new drugs.
- Drug delivery, with targeted delivery and translocation of active therapeutic reagents.

New devices are strongly being established to overcome the low bioavailability of drugs administered orally [12-14]**.** Sufficient adhesion of these devices onto mucous surfaces is significant in achieving effective drug release over a prolonged period. For example, microsized silica beads covered with silicon nanowires provide excellent applicants for adhesive drug delivery devices. This is due to loading with drug suspensions through the capillary effect and interlinks with and sterically attach to apical microvilli on the surface of epithelial cells [15-17].

In addition to improving the ability of drug delivery carriers to adhere to the apical side of the epithelium, it would be desirable to expand the intercellular junctions and enable more effective paracellular

transfer of the drug across the intestinal epithelial barrier.

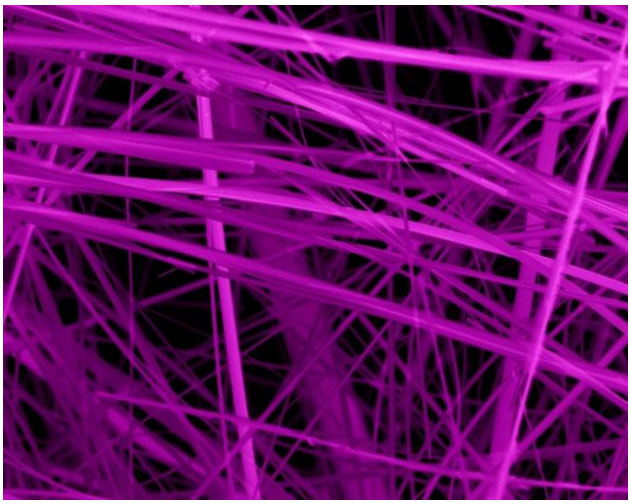

Figure-1: Shows structure of nanowires

SYNTHESIS METHODS

Synthesis of Nickel nanowire:

Ni NWs were produced by a template-assisted electrochemical deposition method (Fig. 2). Anodic aluminium oxide (AAO) membranes comprising ordered channels with pore sizes of about 100 nm or 200 nm that were used as templates. The length of the NWs is controlled by the electroplating time. FESEM (Field emission scanning electron microscopy) micrograph of Ni NW arrays fixed in an AAO template [18-19]. The magnetic properties of the Ni NW arrays fixed in AAO templates were distinguished by a vibrating sample magnetometer.

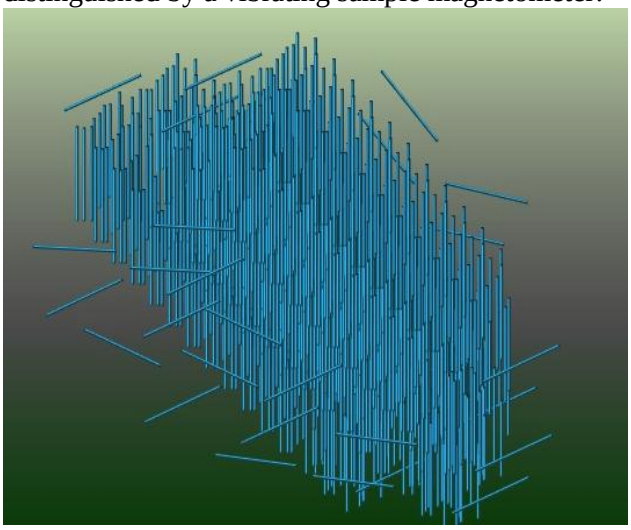

Figure-2: Shows structure of Nickel nanowire

Three orthogonal Helmholtz coil pairs were made in order to generate a uniform rotating magnetic field so there will be a precise control of motion of the Ni NW under an optical microscope. 15 mT can be applied as the maximum magnetic field strength. However, almost 1-3 Mt of the magnetic field strengths is sufficient to complete most cell manipulation tasks.

A Ni NW suspension in DI water was prepared before the magnetic actuation that requires 15-minute sonication and the suspension is transferred into a tank that having the dimension of 20 mm (length) × 15 mm (width) × 2 mm (height).

A Si substrate covered with a SiO_2 layer was positioned at the bottom of the tank for the tests. Once the NWs sank near the Si substrate, the magnetic field was switched on. The Ni NWs will rotate instantaneously in the same plane as the plane of rotation of the magnetic field once the rotating magnetic field is switched on where the nickel nanowire can be operated by the induced magnetic torque (τm) that can make them to be align their long axis to the field.

The magnetic torque for a magnetic NW is stated as: $\tau m = VM \times B$ where V is the volume of the NW, M is the magnetization of the NW and B is the magnetic field in a uniform field. The steering of a NW is by changing the plane of rotation of the applied magnetic field. [18]

Synthesis of Nickel ferrite nanowires:

$NiFe_2O_4$ nanowires were prepared by a co-precipitation synthesis route (Fig. 3). The 0.4 M (20 mL) solution of iron nitrate ($Fe(NO_3)3{\cdot}9H_2O$) and 0.2 M (20 mL) solution of nickel nitrate ($Ni(NO_3)2{\cdot}6H_2O$) were prepared and vigorously mixed under magnetic stirring for 1 h at 80 °C.

Then two different amounts of PEG (0.4 g and 0.2 g) solution were added. Subsequently, 5 mL of hydrazine hydrate was added drop by drop in to the solution to maintain the pH 11 and black colour $NiFe_2O_4$ precipitate was formed. Finally, the $NiFe_2O_4$ nanoparticles were divided by centrifugation and dried in hot air oven for 4 hours at the temperature of 100 °C. The acquired substance was hardened for 10 h at 300 °C then ground into a fine powder. The final samples were completed by different techniques such as powder XRD, microRaman, HR-SEM, TEM, HR-TEM and room temperature VSM **[20].**

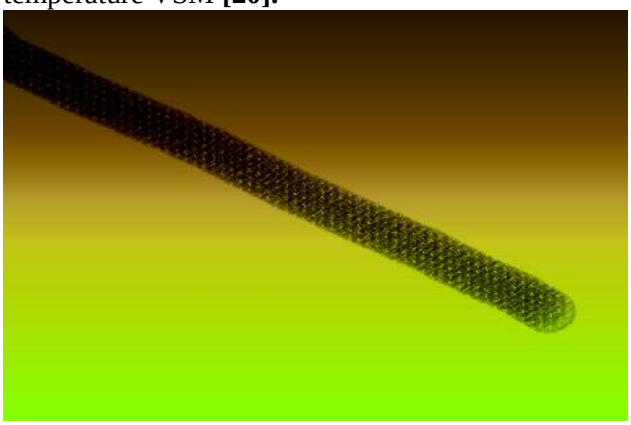

Figure-3: Shows structure of Nickel ferrite nanowires

Synthesis of Silicon nanowire:

HF-assisted etching method can be used for the invention of free silicon nanowire arrays (SiNW). [21-27, 28,29]**.** Firstly, ultrasonic treatment is used for Si wafer where it is treated in acetone solution for 10 minutes. Then, it undergoes washing with Milli-Q water for 3 times. Thereafter, the silicon wafer is immersed in a mixture solution (H_2SO_4 (98%) and H_2O_2 (30%), v/v ¼ 3:1) for half of an hour again it is washed with Milli-Q water for three times. The resultant Si wafer formed is reacted with HF solution (5%) for 30 min thus it produces the hydrogen terminated Si wafer (HeSi wafer). Then immediately the as-prepared HeSi wafer is immersed in a mixture solution of [$AgNO_3$ and HF (10%)] with slow stirring. This can be carried out for 6 minutes in order to produce SiNW arrays on the surface of Si wafer (Fig. 4). In order to separate the as-prepared SiNWs, again it was undergone ultrasonic treatment.

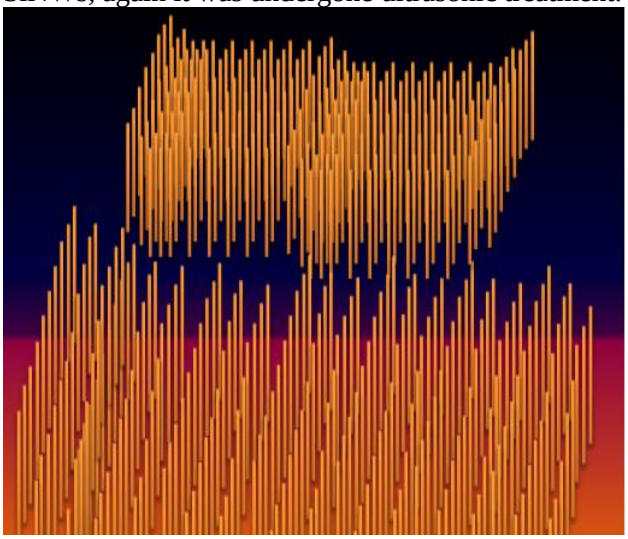

Figure-4: Shows structure of Silicon nanowire

Synthesis of FePd nanowires:

FePd nanowires undergone functionalization process by referring to the method [30]. FePd nanowires at 100 µg/ml were sonicated in hexane with 10 µg/ml oleic acid (OA)for 30min, excess OA was separated by centrifugal washing(2000g) in hexane. FePds were handled in sterile conditions and sterile solutions. Hydrophilic coating was attained by adding 0.5ml of 10mg/ml FePd–OA in hexane to 20ml of 0.5mg/ ml Pluronic-F108 (PF) (SigmaAldrich) in H_2O. By water bath sonication dispersion was found, subsequently hexane was evaporated. PF was granted to adhere overnight under stirring.

Excess Pluronic-F108 was evacuated by washing (2000g) three times in sterile H_2O. To label the FePd fluorescent Nilered (NR) (Sigma Aldrich) was dissolved in 1mg/ml in DMSO and 100 µl was added to10ml of FePd-OA PF at 1mg/ml in H_2O. To let partitioning of the NR into the OA layer nearby the FePd the solution was stirred overnight. FePd were washed five times in Sterile H_2O pursued by two washings in sterile PBS (SigmaAl-drich). Labelling was examined by fluorescence microscopy (Fig. 5).

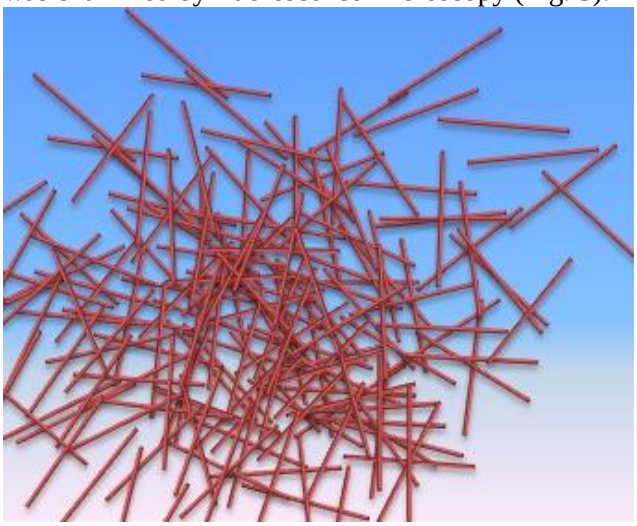

Figure-5: Shows structure of FePd nanowires

EVALUATION OF NANOWIRES

MicroRaman study:

$NiFe_2O_4$ has the space group of Fd3m O^7h. In this structure, half of the Fe^{3+} cations are located on tetrahedral A-site and another half is in form of Fe^{3+} and Ni^{2+} cations in which it is spread over the octahedral B-site. Based to the space group symmetry and factor group analysis, five Raman active internal modes such as A1g, 2Eg and T2g models are concluded. The modes from tetrahedral and octahedral sites can be noted by Raman spectroscopy. Raman peaks over the region of 660–720 cm−1 symbolise the tetrahedral modes in the ferrites, whereas the 460–640 cm^{-1} correspond to the modes of the octahedral sites [31].

HR-SEM, TEM and HR-TEM study:

The uniform aliphatic like structure of PEG-2000 allows it to be absorbed easily metal oxide surface and hence the overall surface energy of the whole system decreased [32]. The orientation aggregation of primary spherical nanoparticles includes the self-assembly of adjacent particles in a common crystallographic orientation joined at planar interfaces of the nanoparticles. $NiFe_2O_4$ nanowires were made by strong adsorption of PEG at certain crystallographic facets which develop the oriented aggregation of nanoparticles. The polycrystalline $NiFe_2O_4$ nanowires continue to grow driven by crystal packing force and stacking interaction between adjacent atoms [33].

Analysis of the nanowires was implemented with a ZeissHR-LEO 1550 FEG Scanning Electron Microscope (SEM) working at 2.0kV. Transmission electron microscopy (TEM) was executed on a Philips CM300ST-FEG Transmission Electron Microscope. Magnetic Characterisation was completed using a vibrating sample magnetometer

(Model 10MarkIIVSM, Microsense**).** The samples obtained were, measured either using the synthesis membrane method or in a glass container where the sample is dried. Before the measurement taken, as empty substrate considered as blank are taken to be deducted from the sample data. [34]

UTILISATION OF NANOWIRES

Living cells:

McKnight et al., (2003) investigate the array of conically shaped carbon nanostructures with tip diameters in the range of 30 nm and lengths of 7 m were functionalized with plasmid DNA encoding green fluorescent protein (GFP).Chinese hamster ovary (CHO) cells was forced onto this array by centrifugation and by subsequently applying pressure. Scanning electron micrographs revealed that the CHO cells were penetrated by the nanostructures, but only a transfection efficiency of less than 1% was achieved [35].

Kim et al., developed cultured human embryonic kidney (HEK293) cells and mouse embryonic stem (mES) cells directly on an array of silicon NWs. One hour after deposition of cell suspension the wires were shown to penetrate the cells. The viability was seen to increase with decreasing diameter of the NWs, consistent with the intuition that a smaller diameter will create less stress when penetrating the lipid bilayer [36].

Hallstrom et al., [37] discussed on mouse neurons cultured on a surface of vertically aligned galliumphosphide (GaP) NWs. The neurons had an even better adherence and a higher viability on a GaP-NW surface compared to a planar GaP surface. Although it is surprising that cells should have higher viability on a surface of nanoneedles, it could be an indication that the roughness of the nanostructured surface improves the adherence and thereby the viability, as seen for some other mammalian cell types [38,39].

DNA delivery:

Kim et al., discussed that possible to coat arrays of silicon NWs with DNA encoding GFP and use its fluorescence to estimate the efficiency of DNA transfection [36].The protein was correctly expressed in the cells, indicating that the DNA was transferred from the wires to the nucleus. The limited transfection efficiency observed can most probably be improved by delivering the DNA directly in the nucleus and increase the quantity of DNA delivered to the cell. This is likely to be achievable because it has already been shown that it is possible to penetrate the nuclear envelope with a nanoneedle maneuvered by an atomic force microscope (AFM) [40]. An advantage of using a NW array as a delivery platform compared to, for example, nanoparticles in solution is that the array provides spatial control of the delivery. This could be used, for example, for parallel delivery of several DNA constructs, while keeping track of which population of cells received what type of DNA. The size of a DNA molecule being quite considerable, translocation of smaller sized molecules or particles, including proteins such as antibodies, can easily be predicted. Such application has not yet been demonstrated on arrays of NW, but the chemical functionalization of NWs with various chemical groups and proteins, including antibodies, is already possible [41]. Using arrays of NWs incorporated in cells with a controlled density and location, delivery of various types of molecules in the cell becomes possible (Fig 6).A few examples of this application *in vitro* appeared recently [42,36] and evidently show the feasibility of using functionalized NWs for the release of compounds in cells.

A Biosensing Platform in Living Cells:

Current fluorescence-based sensors rely on the loading of cells with environment-sensitive fluorescent dyes. Some technical limitations regarding the efficiency and reproducibility of loading the dyes in the cell have been partly solved using translocated particles grafted with well-defined numbers of dyes [43]. Arrays of NWs can be used similarly to those particles because they can be functionalized with multiple compounds [41] (Fig 7). Moreover, as discussed earlier, the NWs can be made from different materials and doped with other elements or coated with protective or active layers; this opens up opportunities for the design of sensors with novel intrinsic properties to be directly exploited for cellular sensing.

The geometry of NWs and their immobilization on surfaces present two additional advantages compared to existing sensors: control of the number of sensors per cell and location of the sensors in the cell (Fig.7), allowing a three-dimensional mapping of cellular events. This would especially be relevant within neuroscience for mapping signal propagation in a single nerve cell, but also in neuronal networks [44, 43].

Electrophysiology in a Cell Using Arrays of Nanowires:

In 2006, McKnight et al., developed an array of individually contacted electrically active carbon nanofibers (CNF) on a silicon surface. This publication makes it reasonable to start looking into the application of NWs as nanoelectrodes in electrophysiology measurements (Fig 8).With this device McKnight et al., succeeded in getting electrical responses from oxidative events occurring in intercellular regions of a neuronal culture that had been cultured directly on the nanofibers [45].

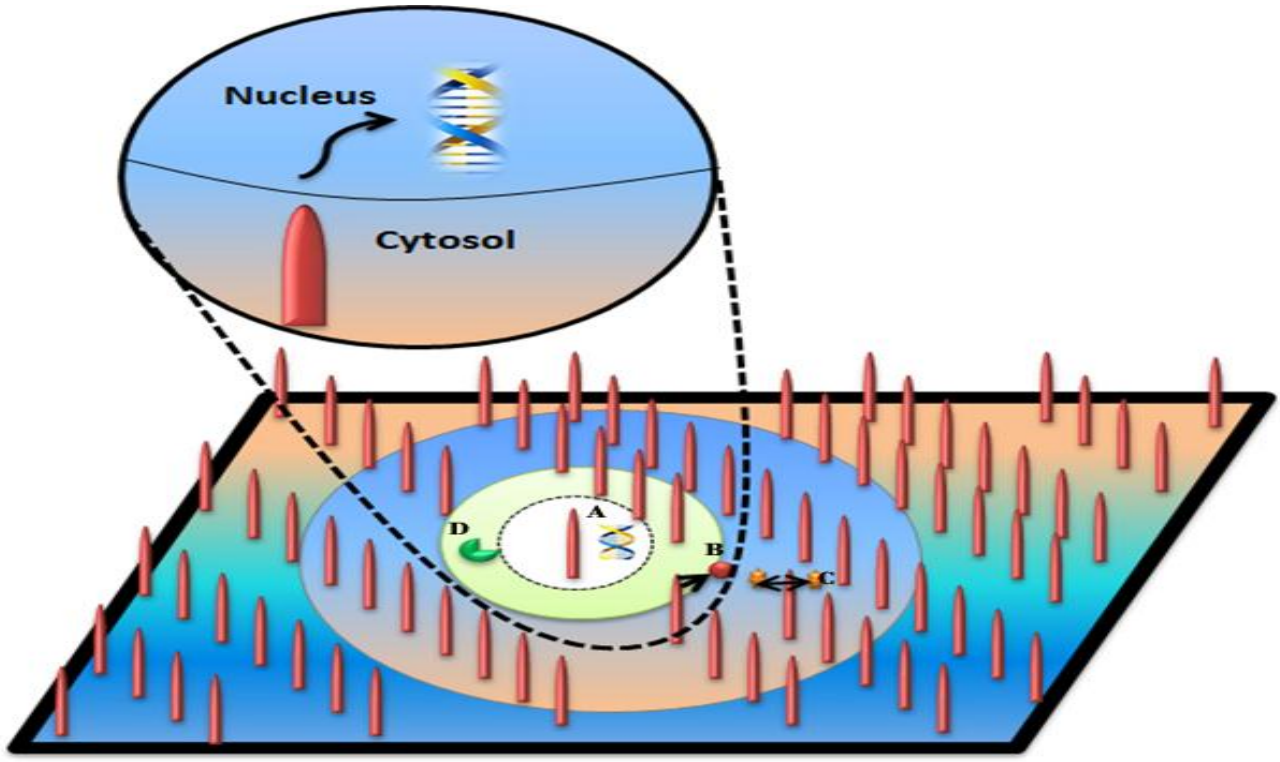

Figure-6: Present and future applications of NW arrays interfaced with living cells: Delivery platform. Cell on a NW array illustrating the potential as delivery and detection platform for DNA (A), particles (B,C) and proteins (D).NWs have small enough dimensions to enable direct delivery into the nucleus.

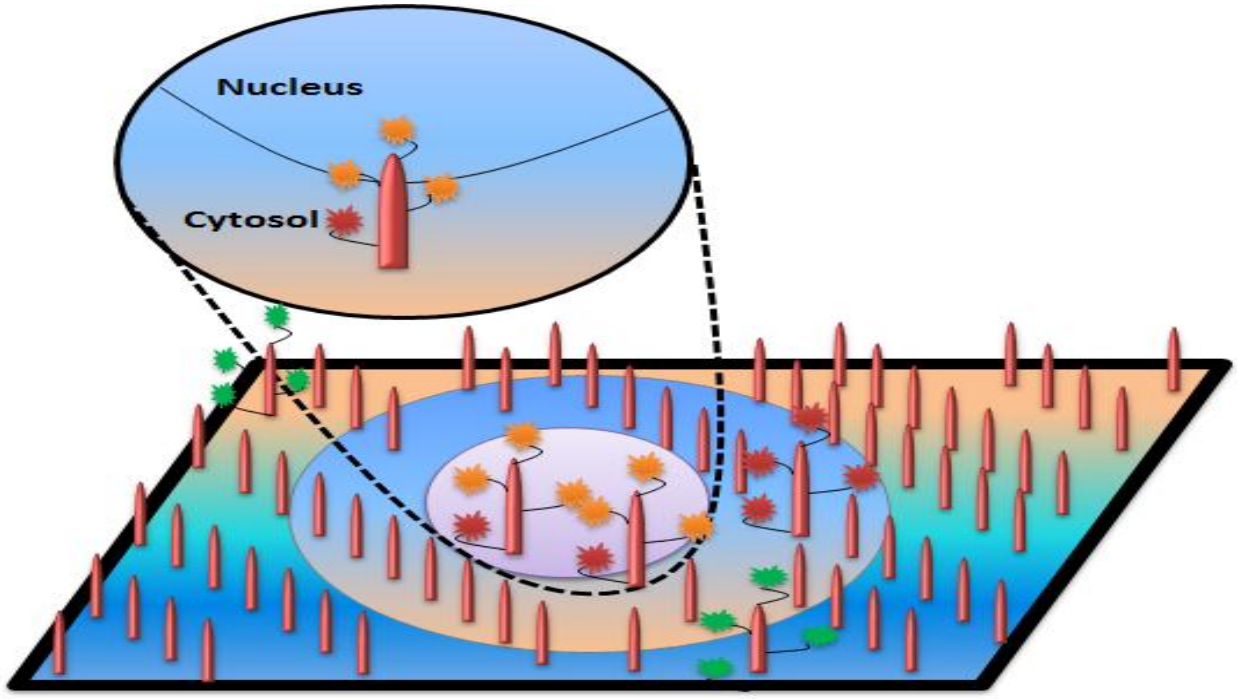

Figure-7: Present and future applications of NW arrays interfaced with living cells: Biosensor.Cell on a NW array illustrating the potential as a fluorescence biosensor. NWs can be functionalized with environmentsensitive fluorophores (orange, red, green) and provide spatially resolved information both within a single cell and in networks of cells.

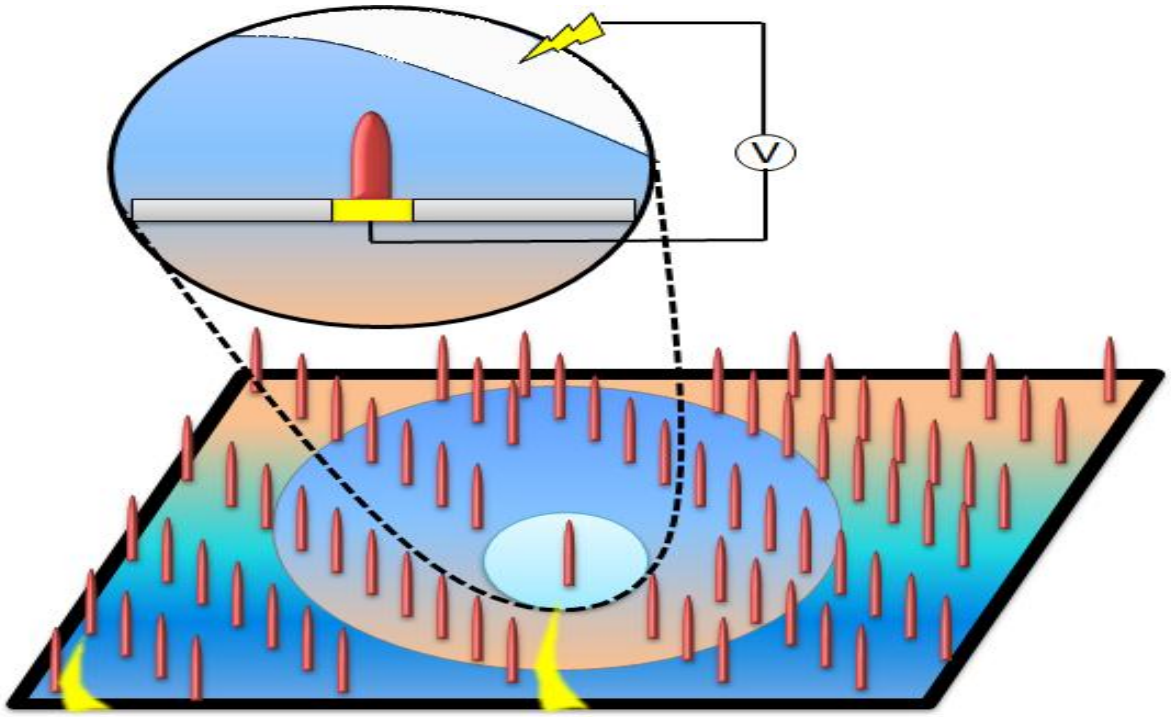

Figure-8: Present and future applications of NW arrays interfaced with living cells: Electrophysiology. Cell on NW array illustrating the potential of NWs as intra- and extracellular nanoelectrodes in electrophysiology. Each NW can be electrically contacted through the surface (yellow).Changes in whole-cell potential are measured as a change in potential with respect to a standard-size extracellular counter electrode (yellow triangle). The array enables single-cell measurements on multiple cells simultaneously, representing future applications for HTS of drugs that target ion channels

A widely used tool in neuroscience is the patch clamp technique, used for measuring the activity of ion channels in the cell membrane. In traditional whole-cell patch clamp measurements intracellular access is attained by rupturing the cell membrane by means of applying suction pulses to a pipette attached to the cell membrane. After the cell membrane is broken, the saline solution in the pipette intermixes with the cytosol of the cell causing a change in the balance of the cell's intracellular solution. This change affects the function of ion channels and reduces the lifetime of the cell.

CONCLUSION

Nanowires emerge to be favorable tools for nanomedicine, with a multitude of putative applications in drug delivery, diagnostics, and high-throughput screening of new molecules. The potential of nanowires apply to a significant range of cell types, with numerous adhesion properties, suggesting that such nanowires can be adapted to a variety of cell cultures and tissues. The first set of applications concerns *in vitro* study of cell cultures or isolated tissues for fundamental investigation of cellular signaling and cell/cell communication, nevertheless also the design of novel high-throughput screening strategies for novel potentially therapeutic compounds or diagnostics on biopsies. A second set of upcoming applications concerns use of nanowires in human tissue for innovative therapies.

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